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Impact of diabetes duration and cardiovascular risk factors on mortality in type 2 diabetes: the Hoorn Study

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Abstract

Background Several studies have reported differences in the mortality risk between diabetic subjects detected by screening and known diabetic patients. We studied mortality in relation to diabetes duration, and the contribution of other cardiovascular risk factors to the elevated risk.

Materials and methods Participants were type 2 diabetic subjects ($n = 174$) of a population-based cohort study. Of these, 95 were diagnosed by screening. Known diabetic subjects were grouped into two categories of diabetes duration, with a median duration of 2·4 and 11·2 years, respectively. We assessed the contribution of classical cardiovascular risk factors (dyslipidaemia, hypertension, and prior myocardial infarction), and of new cardiovascular risk factors (microalbuminuria, von Willebrand factor, sVCAM-1 and C-reactive protein) to the mortality risk during nearly 10 years of follow up. Cox's proportional hazards model was used to study the association of diabetes duration and mortality.

Results The age- and sex-adjusted relative risks of mortality were 2·06 (95% C.I. 1·04–4·10) and 3·19 (1·64–6·20) for the patients with short- and long-term diabetes compared with the screening-detected diabetic subjects, respectively. Adjustment for cardiovascular risk factors resulted in a reduction of mortality risk in both groups: 1·13 (0·51–2·50) and 2·39 (1·18–4·83), respectively. Mortality risk significantly increased with increasing diabetes duration, even after multiple adjustment (*P*-value for trend ranged from < 0·001–0·018).

Conclusions Mortality risk increased with increasing diabetes duration. In subjects with short diabetes duration the mortality risk could largely be attributed to other risk factors. In subjects with a longer diabetes duration, however, the elevated mortality risk was independent of these cardiovascular risk factors.

Keywords Diabetes duration, mortality, risk factors, type 2 diabetes.
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Introduction

Some longitudinal studies have shown that mortality risk is higher in known diabetic patients as compared with patients detected by (population) screening [1,2]. In view of the current debate about screening for type 2 diabetes [3], it would be helpful to know the explanation for this difference in mortality risk. Difference in diabetes duration seems to be an obvious candidate, but the results are inconsistent. Data from the Whitehall Study and the WHO Multinational Study of Vascular Disease in Diabetes [4,5] failed to show any relation between diabetes duration and mortality risk. In contrast, other studies have shown higher mortality risk for a longer diabetes duration [2,6,7]. In a small Finnish study, the association was independent of known cardiovascular risk factors [2].

Longer diabetes duration is associated with an increased prevalence of classical cardiovascular risk factors (hypertension, dyslipidaemia, and prevalent heart disease), which may partly explain the elevated mortality risk. In addition, a longer duration of diabetes implies longer exposure to chronic hyperglycaemia, with its deleterious effect on small

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and large vessels [8]. Markers of endothelial dysfunction, such as microalbuminuria, von Willebrand factor and soluble vascular adhesion molecule-1, and markers of low-grade inflammation, like high levels of C-reactive protein, have been postulated as 'new' cardiovascular risk factors [9]. These new risk factors may also partly explain the association of diabetes duration with mortality risk.

In view of these considerations, we addressed the question of whether diabetes duration is associated with increased mortality risk, independently of classical and new cardiovascular risk factors. The question was addressed in the Hoorn Study, a population-based cohort study of glucose intolerance with a follow up of nearly 10 years.

Methods

Population

The Hoorn Study is a population-based cohort study of glucose intolerance in a Caucasian population aged 50–75 years. Baseline examinations were conducted from October 1989 until February 1992, as previously described [10]. Briefly, all 2484 subjects, except previously diagnosed diabetic subjects treated with oral glucose-lowering agents or insulin, underwent a 75-g oral glucose tolerance test. Subjects with a 2-h glucose $\geq 7{\cdot}5$ mmol L^{-1}, all type 2 diabetic subjects and a random sample of subjects with a 2-h glucose $< 7{\cdot}5$ mmol L^{-1} stratified for age and sex were invited for a second oral glucose tolerance test (OGTT). An extensive medical examination was performed in an age- and sex-stratified sample of 631 subjects [11]. The present analyses were carried out in all diabetic subjects of this sample ($n = 174$). Subjects who were already treated for diabetes (diet, oral hypoglycaemic agents or insulin) were classified as having known diabetes (KDM, $n = 79$). Subjects detected with diabetes by means of the OGTT were considered to have screening-detected diabetes mellitus (SDM, $n = 95$). The WHO diagnostic criteria of 1985 were applied to the mean fasting and mean 2-h glucose values of the two OGTTs [12]. All participants gave informed consent for this study, which was approved by the local Ethics Committee.

Measurements

Information about the duration and family history of the diabetes was self-reported and collected by means of a questionnaire. Duration of diabetes was defined as the time from diagnosis to study entry. Diabetes duration was not distributed normally as the duration of all diabetic patients detected by screening was zero, while the duration in the group of known diabetic subjects ranged from approximately 3 months to 29 years. In the known diabetic patients, the median of diabetes duration (6·2 years) was used as a cut off to form two groups. One group included known diabetic patients with short diabetes duration (median 2·4 and range 0·3–6·2 years), the other group consisted of patients with long diabetes duration (median 11·2 and range 6·3–29·0 years). Family history of diabetes was considered positive if any of the subject's grandparents, parents, siblings or children had a history of diabetes. We obtained data on blood pressure, weight, height, body mass index (BMI) and smoking habits, and performed an ECG recording [13,14]. Subjects were considered to have hypertension with diastolic blood pressure ≥ 95 mmHg, systolic blood pressure ≥ 160 mmHg, and/or when using antihypertensive medication (i.e. the definition in use when baseline data were collected). Prior myocardial infarction was considered present when the ECG recording contained Minnesota codes 1·1–1·2. Current smoking was defined as currently smoking cigarettes or cigars. We also obtained information about fasting and 2-h plasma glucose, glycated haemoglobin, serum total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol) levels and triglycerides [13,14]. High serum total cholesterol was defined as $> 5{\cdot}0$ mmol L^{-1}, low HDL-cholesterol as $< 1{\cdot}0$ mmol L^{-1}, elevated LDL-cholesterol as $\geq 3{\cdot}0$ mmol L^{-1} and high triglycerides as $> 2{\cdot}0$ mmol L^{-1} [15].

Urinary albumin was measured by rate nephelometry (Array Protein System, Beckman, Galway, Ireland) [11]. Urinary creatinine was measured by a modified Jaffé method. Subjects were classified as having (micro)albuminuria when they had a urinary albumin concentration above the assay threshold (6·2 mg L^{-1}) and an albumin-to-creatinine ratio of $> 2{\cdot}0$ mg $mmol^{-1}$ both for the men and the women [11]. Von Willebrand factor concentrations were assessed, in duplicate, in heparin plasma by ELISA with polyclonal antibodies from Dako (Glostrup, Denmark), and expressed as a percentage of von Willebrand factor in pooled plasma of the healthy volunteers [16]. Concentrations of soluble vascular adhesion molecule-1 (sVCAM-1) were measured, in duplicate, by enzyme-linked immunosorbent assay kits (Bender MedSystems, Vienna, Austria [Cat.#BMS232]) as described previously [17]. C-reactive protein levels (CRP) were assessed, in duplicate, with an EIA that used rabbit antibodies to C-reactive protein (Dako) as both the capture and tagging antibody [18]. High CRP was defined as a level of 2·84 mg L^{-1} or greater [14].

Follow up

Data on the subjects' vital status on January 1st 2001 were collected from the registry office in the city of Hoorn or elsewhere for those who had moved out of Hoorn [1]. For all participants who died, the cause of death was extracted from the medical records of the general practitioner and the hospital of Hoorn and classified according to the ninth edition of the International Classification of Diseases [19]. As a small number of subjects died of cardiovascular disease ($n = 25$), only all-cause mortality was considered in this paper.

Statistical analyses

Baseline characteristics were compared between categories of diabetes duration. For continuous variables we used a test

for a linear trend within an analysis of variance, adjusted for age and sex. Logistic regression analysis was used for binary variables. To study survival, Kaplan–Meier curves were plotted for the SDM and KDM subjects with diabetes of short and long duration. Differences in survival were tested by a log-rank test for linear trends. Cox proportional hazards multiple regression analyses were used to investigate the association between diabetes duration and mortality. Results are described as relative risks (hazard ratios) and 95% confidence intervals, with the screening-detected diabetic patients as the reference group. A test for trend was used to determine whether mortality risk significantly increased over the three categories of diabetes duration. Proportional hazards assumptions were tested with the inclusion of a time-dependent variable, which showed that these assumptions were not violated. Variables measured on a continuous scale were used as such in the regression analyses, except for triglycerides, total cholesterol, HDL-cholesterol and CRP-levels, as the association of these variables with mortality was nonlinear. These variables were dichotomized according to the cut-off points described earlier.

Selection of variables to be included in the multivariate analyses was based on the change in estimate approach [20]. All variables that were thought to possibly play a role in the association between diabetes duration and mortality were examined in the Cox regression analyses, all adjusted for age and sex. Those variables that resulted in a change of the relative risk of mortality associated with diabetes duration of 10% or more were examined again in the multivariate analyses. Only those variables that changed the relative risk with 10% or more in the multivariate model were included in the final model. All analyses were performed with the SPSS for Windows version 10·1·1 software (SPSS Inc., Chicago, IL, USA). All *P*-values were based on two-sided tests and a *P*-value of $< 0{\cdot}05$ was considered to be statistically significant.

Results

The population consisted of 174 subjects (98 women, 76 men) with a mean age of 66 (± 7) years (Table 1). Treatment of diabetes in the KDM patients consisted of a diet in 12 subjects, oral hypoglycaemic agents in 52 subjects and insulin in 15 subjects. Fasting plasma glucose and HbA1c levels

Table 1 Baseline characteristics in the categories of diabetes duration

		KDM	
Diabetes duration categories	SDM	Short duration	Long duration
n	95	40	39
Age (year)	66 (7)	67 (6)	64 (7)
Gender (M/F)	45/50	12/28	19/20
Diabetes duration (year)	0	2·4 (1·3–5·0)	11·2 (7·7–15·9)
Family history of diabetes (%)	37	48	68*
Fasting plasma glucose (mmol L^{-1})	8·3 (3·1)	9·7 (3·3)	11·7 (3·7)*
HbA1c (%)	6·7 (1·9)	7·4 (1·6)	8·2 (1·5)*
High total cholesterol (%)	86	90	85
Low HDL-cholesterol (%)	32	28	23
High LDL-cholesterol (%)	89	92	91
High triglycerides (%)	50	46	44
BMI (kg/m*m)	28·8 (4·2)	28·8 (4·9)	28·8 (5·3)
Hypertension (%)	51	63	62
Prior myocardial infarction (%)	1·1	12·5	5·1
Current smoking (%)	23	23	28
Microalbuminuria (%)	10	33	42*
VWF (IU mL^{-1})	1·60 (0·80)	1·57 (0·83)	1·77 (0·63)
SVCAM-1 (ng mL^{-1})	1442 (458)	1683 (758)	1509 (533)
High CRP (%)	44	42	49
Deaths, *n* (%)	24 (25)	16 (40)	17 (44)

Data are presented as means (SD), median (interquartile range) (diabetes duration) or percentages.

Diabetes duration categories were defined as subjects with screening-detected diabetes mellitus (SDM), known diabetic patients with diabetes duration ≤ 6·2 years (KDM short duration), and known diabetic patients with diabetes duration > 6·2 years (KDM long duration). High total cholesterol was defined as serum total cholesterol > 5·0 mmol L^{-1}; low HDL-cholesterol as HDL < 1·0 mmol L^{-1}; elevated LDL-cholesterol as ≥ 3·0 mmol L^{-1} and high triglyceride level as > 2·0 mmol L^{-1}. Hypertension was defined as diastolic blood pressure ≥ 95 mmHg, systolic blood pressure ≥ 160 mmHg, and/or use of antihypertensive medication; and prior myocardial infarction as Minnesota codes 1·1–1·2 in ECG recording. Family history of diabetes was considered positive if any of the subject's grandparents, parents, siblings or children had a history of diabetes. Current smoking was defined as currently smoking cigarettes or cigars. Microalbuminuria was defined as albumin-to-creatinine ratio of > 2·0 mg $mmol^{-1}$; and high C-reactive protein (CRP) as CRP > 2·84 mg L^{-1}. BMI, body mass index; VWF, von Willebrand factor; sVCAM-1, soluble vascular adhesion molecule-1.

*P-value for trend < 0·05.

increased with diabetes duration, and were highest in the long diabetes duration group. Family history of diabetes and (micro)albuminuria also showed a significant trend over categories of diabetes duration. The prevalence of prior myocardial infarction was highest in the short diabetes duration group as were sVCAM-1 levels. During nearly 10 years of follow up, 57 (33%) subjects died. Among the SDM subjects, 25% died compared with 40% and 44% in the groups of short and long diabetes duration, respectively.

Figure 1 shows the Kaplan–Meier survival curves for categories of diabetes duration. Mortality significantly increased with a longer diabetes duration (log-rank test for linear trend, $\chi^2 = 5{\cdot}23$, P-value = 0·02). Testing of cardiovascular risk factors showed that microalbuminuria, prior myocardial infarction, sVCAM-1 levels and family history of diabetes changed the relative risk of diabetes duration with more than 10% in the Cox regression analyses. Other risk factors did not result in a 10% change and were not included in the multiple regression models.

Table 2 shows the results of the multivariate survival analyses. Mortality risk increased with increasing diabetes duration (model 1) and this effect was also observed after adjustment for various cardiovascular risk factors and family history of diabetes (models 2–5). Simultaneous adjustment for (micro)albuminuria, prior myocardial infarction and sVCAM-1 resulted in a reduction of relative risk in both categories of diabetes duration (model 6). The risk estimate in the group with long diabetes duration was reduced, but remained elevated. Additional adjustment for family history of diabetes (model 7) resulted in an increase in relative risk (1·18 and 2·92, respectively). The increase in mortality risk with increased diabetes duration showed a statistically significant trend in all models.

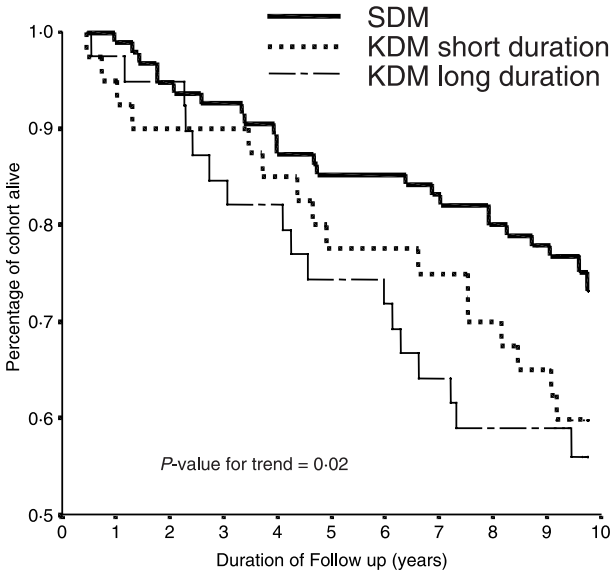

Figure 1 Survival (Kaplan–Meier) curves according to categories of diabetes duration. SDM, screening-detected diabetic patients; KDM, short duration: known diabetic patients with duration ≤ 6·2 years; KDM, long duration: known diabetic patients with duration > 6·2 years.

We investigated whether the definition of the diabetes duration groups affected the results. When the diabetes duration was divided into tertiles and the screening-detected diabetic patients were used as a reference group, the association between diabetes duration and mortality also showed a significant trend. This significant trend was also present after multiple adjustment (data not shown).

Discussion

This study shows that mortality risk rises with increasing diabetes duration. In the diabetic subjects with long diabetes duration the association with mortality risk was independent of cardiovascular risk factors. However, in the subjects with short diabetes duration, the association could largely be attributed to cardiovascular risk factors.

Diabetes duration since diagnosis, the variable of principal interest in this study, is clearly an underestimation of the actual duration of the disease, because a diagnosis is never made at the actual start of hyperglycaemia in the diabetic range. Patients detected by screening may be nearer the true onset of diabetic hyperglycaemia as they are asymptomatic at the time of the diagnosis. In known diabetic patients, who do present with symptoms and signs at diagnosis, this underestimation of the diabetes duration might be worse.

The lower risk in the SDM subjects may also partly be explained by length-time bias associated with screening [21]. Length-time bias means that those with a more serious type of diabetes will present with symptoms and signs and will be detected accordingly, independent of screening. In the remaining population at risk for diabetes, people with a relatively mild form of diabetes with a slower progression and better prognosis are over-represented, and will be detected by screening. This way, mortality risk in patients with screening-detected diabetes mellitus might be lower, not because of the shorter diabetes duration, but because they have a more 'benign' type of diabetes. On the other hand, after adjustment for cardiovascular risk factors, known diabetic patients with short duration had a mortality risk similar to that of screening-detected diabetic patients, a result that does not seem to support the 'benign type of diabetes explanation.

Population size and the relatively small number of events in this study restricted the number of variables that could be included in the Cox regression models. Therefore, other risk factors that might play a role in the association between diabetes duration and mortality might have been missed. In addition, factors that were not measured in our study such as small dense LDL particles might explain part of the association.

The lower prevalence of high cholesterol levels and low HDL-cholesterol and sVCAM-1 levels and prior myocardial infarction in the group with long diabetes duration might be indicative of a 'healthy survivor effect'. Subjects with diabetes and multiple risk factors for heart disease have a high risk of having already died, before reaching old age

Table 2 Relative risks (95% confidence intervals) for categories of diabetes duration relative to the subjects with screening-detected diabetes mellitus

	Relative risk (95% CI)		
Cox regression models (SDM, reference group: n = 90, 21 events)*	KDM: short duration (n = 36, 14 events)*	KDM: long duration (n = 37, 17 events)*	P-value for trend†
Model 1: age and sex	2·06 (1·04–4·10)	3·19 (1·64–6·20)	< 0·001
Model 2: model 1 + microalbuminuria	1·79 (0·88–3·67)	2·66 (1·30–5·41)	0·006
Model 3: model 1 + prior myocardial infarction	1·68 (0·82–3·46)	3·03 (1·56–5·92)	0·001
Model 4: model 1 + sVCAM-1	1·69 (0·83–3·43)	2·94 (1·51–5·71)	0·001
Model 5: model 1 + family history diabetes	2·18 (1·09–4·37)	4·25 (2·07–8·71)	< 0·001
Model 6: model 1 + microalbuminuria + prior MI + sVCAM-1	1·13 (0·51–2·50)	2·39 (1·18–4·83)	0·018
Model 7: model 6 + family history of diabetes	1·18 (0·53–2·64)	2·92 (1·36–6·27)	0·008

Diabetes duration categories were defined as subjects with screening-detected diabetes mellitus (SDM), known diabetic patients with diabetes duration ≤ 6·2 years (short duration KDM), and known diabetic patients with diabetes duration over 6·2 years (long duration KDM).

Prior myocardial infarction (prior MI) was defined as Minnesota codes 1·1–1·2 in ECG recording. Family history of diabetes was considered positive if any of the subject's grandparents, parents, siblings or children had a history of diabetes. Microalbuminuria was defined as albumin-to-creatinine ratio of > 2·0 mg mmol^{-1}. sVCAM-1, soluble vascular adhesion molecule-1.

*Numbers and events reduced because of missing data for some variables included in the analyses.

†To test whether mortality risk significantly increased over the three categories of diabetes duration.

and a longer diabetes duration. However, if this healthy survivor effect were present, a relatively low mortality risk in the survivors would be expected. But this was not observed, and despite the possibility of this healthy survivor effect we found the association between mortality and long diabetes duration to be statistically independent of other risk factors.

The results of our study are in line with some [2,6,7,22,23] but not all published studies [4,5] concerning the association between diabetes duration and mortality. All previous studies differed in one or more of the following aspects from our study: end-point (CHD vs. all-cause) [2], duration of follow up [2,4,6,7,22,23], age-distribution [2,4–7,22,23] and sex-distribution [4,22] of the population. In most other studies, diabetes duration was divided into categories of 5 years of duration and newly diagnosed subjects were included in the category with the shortest duration (< 5 years) [2,6,7,22]. In these studies the diagnosis of diabetes was based on one OGTT [2,23] or patients were diagnosed by their general practitioner [6,7]. In contrast, in our study, the analyses were performed with the SDM subjects as the reference category, and thus resulted in more precise estimates of mortality risk in diabetic subjects with short diabetes duration. Moreover, the diagnosis of diabetes was based on the mean of two OGTTs, reducing random misclassification as a result of variable glucose levels.

This study is the first prospective study to address the association of diabetes duration with mortality risk not only in the context of classical risk factors but also in the context of new risk factors indicative of endothelial dysfunction or low-grade inflammation. In our study, higher mortality in the short duration group was explained completely by prior myocardial infarction, microalbuminuria and levels of sVCAM-1, but only partly in the group with long diabetes duration. Prior myocardial infarction is a well-known risk factor for mortality in diabetic and nondiabetic individuals [24]. Microalbuminuria also has a well-established association with mortality [25]. Elevated levels of sVCAM-1 have been suggested to reflect the progressive formation of atherosclerotic lesions [26] and to be associated with symptomatic atherosclerotic disease in type 2 diabetic patients [27]. In the Hoorn Study sVCAM-1 was associated with cardiovascular and all-cause mortality independent of other risk factors [17].

Adjustment for family history of diabetes resulted in a higher relative risk, particularly in individuals with long diabetes duration. This effect might be explained by the fact that people with a positive family history are more carefully monitored for diabetes and are diagnosed earlier, and therefore selectively have, on average, longer diabetes duration than patients without a family history. Consequently, after correction, the association of actual diabetes duration with mortality risk is even stronger.

Our results suggest a continuously increasing mortality risk with increasing diabetes duration independent of other risk factors. The underlying pathophysiological mechanism is as yet unclear. Diabetes duration might be a marker of duration of exposure to chronic hyperglycaemia. In this view, the fact that long diabetes duration is an independent risk factor might be reflective of the irreversibility of hyperglycaemia-induced changes in cardiovascular structure and function. This irreversibility has been shown by the observation in some studies, that improved glycaemic control (decrease in HbA1c) does not decrease the concentration of endothelial markers nor haemostatic abnormalities in type 2 diabetic patients [28,29].

In our view, the results of this study indicate either that diabetes duration per se is a strong and independent risk factor for mortality in type 2 diabetic patients or that diabetes duration is reflective of other, yet unknown, potent risk factors. Larger studies are needed to study the

pathophysiological mechanisms underlying the association of diabetes duration and elevated mortality. Other studies will show whether early treatment of hyperglycaemia and cardiovascular risk factors in screening-detected diabetic patients will have any impact on mortality risk.

In conclusion, mortality risk was elevated in the known diabetic patients compared with the screened subjects. Mortality risk associated with diabetes duration was independent of risk factors in the diabetic patients with long duration. In the patients with short duration, the elevated mortality risk associated with diabetes duration could for the most part be attributed to cardiovascular risk factors. These results emphasize the importance of treating cardiovascular risk factors in type 2 diabetic patients.

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